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Atherosclerosis in the Back Yard

Joerg Herrmann, MD, Amir Lerman, MD

Rochester, Minnesota

The phenomenon of neovascularization in atherosclerosis has been widely recognized through "the eyes of novel imaging techniques" in recent years. Oxidative stress, inflammation, and hypoxia have been implied as the underlying mechanisms. The pathophysiologic consequences and therapeutic implications of this neovascularization process for atherosclerosis have, however, remained challenging and controversial. In the current focus issue of the *Journal*, 4 articles and this commentary are devoted to this topic. (J Am Coll Cardiol 2007;49: 2102–4) © 2007 by the American College of Cardiology Foundation

It was not until the end of the 20th century that the phenomenon of neovascularization in atherosclerosis was widely recognized, mainly supported by "the eyes of novel imaging techniques" (1,2). However the reports on this phenomenon form just the introduction to the tale of "angiogenesis in atherosclerosis." The currently expanding, more challenging, and controversial chapters relate to the very process of angiogenesis, its causal relationship with the progression and complication of atherosclerosis, and its therapeutic implications. From vision to therapy, from bench to bedside, this experience may eventually resemble the process of "angiogenesis and the struggle to defeat cancer" (3).

In atherosclerosis, the formation of new vessels around the arterial wall can be seen even before the development of endothelial dysfunction and plaque formation (4). Moreover, vasa vasorum neovascularization evolves mainly in the area of intimal thickening, indicating "cross-talk" between the intima and the adventitia (5). Indeed, this neovascularization process creates a potential entry port for inflammatory and proliferative factors, red blood cells (RBCs), and inflammatory cells from the circulation to the adventitia. In this process, the media and subintimal space become "sandwiched" between 2 highly vascular layers and directly exposed to an extensive endothelial surface area on either side. As the atherosclerotic plaque develops, neovessels "sprout" from the adventitial vasa vasorum through the media into the intima lesion (2). Only a small fraction of the intima vessels can be traced back to the main lumen. The plaque areas that are particularly rich in neovessels include the shoulder region and the base (2,6). Eventually, plaque neovascularization seems to characterize not only the vulnerable plaque but also the vulnerable patient (7). Thus, angiogenesis is an "associate" of atherosclerosis through its various stages.

Given the early onset of vasa vasorum neovascularization in atherogenesis, factors other than hypoxia, classically thought to be the main stimulus for angiogenesis, have to be considered. Increased oxidative stress in the arterial wall may stimulate vasa vasorum neovascularization (8). Inflammation may be another important factor, and there may even be a mutual interaction between vascular inflammation and neovascularization (9). As the atherosclerotic lesion increases in volume, hypoxia may become a more prominent stimulus for neovessel formation (10). At that point, further growth of the atherosclerotic plaques may actually depend on angiogenesis, reminiscent of a cancerous lesion (1). Despite the identification of a number of mechanisms that can contribute to the neovascularization process, our understanding of the regulation of this process in atherosclerosis still remains incomplete (11).

A number of studies indicate that the newly formed vessels are leaky and fragile and for this reason may lead to the extravasation of RBCs and even true intraplaque hemorrhage (12). Given the rich cholesterol content of RBCs, this may contribute to the lipid loading of the atherosclerotic plaque, its progression in volume, and vulnerability. As an additional factor, release of free hemoglobin can stimulate oxidative stress and inflammation in the atherosclerotic plaque (2). The newly formed vessels may contribute to these unfavorable plaque dynamics further by serving as conduits for inflammatory cells and soluble factors (1). Moreover, proteolytic enzyme activity during the neovascularization process may weaken plaque structures, contributing to plaque vulnerability, especially in the shoulder regions (13). Thus, the microvasculature of the plaque may contribute to the progression and

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complication of atherosclerotic disease and may therefore be of therapeutic interest.

A focus series in the current issue of the *Journal* addresses the triad of plaque neovascularization, hemorrhage, and vulnerability. In the first 2 papers in the series, Tziakas et al. (14) report and Arbustini (15) comments on the observation that the total cholesterol content of erythrocyte membranes was more than 2 times higher in patients presenting with acute coronary syndrome than in patients with chronic stable angina. The authors suggest that RBC total cholesterol content may serve as a novel marker for atherosclerotic plaque progression and complication. The diagnostic and prognostic value of RBC total cholesterol for atherosclerotic cardiovascular disease, however, awaits confirmation.

In their viewpoint paper, Kolodgie et al. (16) expand on the contribution of RBC cholesterol to atherosclerotic plaque growth and vulnerability via fragile plaque neovessels. As a logical extension, they introduce the concept of antiangiogenic therapy and highlight the option of local drug therapy, possibly supplied on the platform of coated stents. Doyle and Caplice (17) further review the opportunities and pitfalls of antiangiogenic therapy in the context of atherosclerosis. Both groups agree that a multitargeted approach will most likely be required and call for rigorous experimental evaluation of this new treatment paradigm before clinical trials are considered.

Indeed, there is limited experimental experience with antiangiogenic therapy in atherosclerosis, and the findings have to be interpreted within the framework of a complex interplay of factors in vivo. Nevertheless, the agents that have shown promise include the natural inhibitors endostatin, a 20-kDa fragment released from the collagen XVIII, and angiostatin, an internal proteolytic fragment of plasminogen, as well as synthetic inhibitors such as TNP-470, an analogue of fumagillin, and vascular endothelial growth factor (VEGF) receptor-1 antagonists (18). A therapeutic alternative would be to "simply" target inflammation and oxidative stress, given their pathophysiologic momentum. In fact, the most successful drugs for the treatment of atherosclerosis, which are associated with antiinflammatory and antioxidative activities, have also been shown to exert antiangiogenic effects. Among these drugs are aspirin, HMG-CoA reductase inhibitors, and antagonists of the renin-angiotensin system (19–22). However, specific antiangiogenic agents may be needed to supplement and antagonize the progression and complication of atherosclerosis beyond the accomplishments of these drugs.

Another important aspect in the consideration of antiangiogenic therapy for atherosclerosis is the systemic and focal nature of this disease, leading to the concept of the vulnerable patient rather than a single vulnerable plaque. This raises the question of how we should identify patients who are to benefit from antiangiogenic therapy. For local therapy, this question would have to be extended toward the identification of the vulnerable plaque. Imaging methods are evolving but are not yet validated to allow routine assessment of the neovascularization process in the plaque. This would be required to assess treatment effects, including causality between intervention and outcome. If the interventions were truly catheter-based, a number of technical concerns would have to be addressed. Catheter-based interventions such as stenting lead to a remarkable neovascularization response themselves and harbor the risk of procedure-induced end-organ injury (22–25). The current generation of drug-eluting stents has some antiangiogenic potency; in direct comparison, however, angiostatin inhibits endothelial cell proliferation and neointima formation more strongly than paclitaxel (26). Considering their potency and the likely need for prolonged therapy, systemic (multi-drug) antiangiogenic therapy is burdened with the concern of reducing collateral vessel formation and end-organ neovascularization, two processes of significance for patients with diffuse atherosclerosis. In addition, at least some of these agents may affect not only endothelial cells of new vessels but also endothelial cells of existing vessels. Hypertension, proteinuria, and thrombosis, for example, have been reported with the use of VEGF antagonists and have been attributed to the interference with the physiologic functions of VEGF on the endothelium (18). Finally, the appropriate timing, drugs, and dosing of these therapies are still unknown. Thus, both systemic and local antiangiogenic therapies are associated with a number of uncertainties in target specification, efficacy, and side effects. However, these apparent obstacles should be regarded only as challenges that can be overcome by future studies.

Abbreviations and Acronyms

RBC = red blood cell

VEGF = vascular endothelial growth factor

The next chapter in the book on "angiogenesis in atherosclerosis" has yet to be written, but the miniseries in the current issue of the *Journal* is already an important contribution. Finally, it highlights our preoccupation with the lumen and the significance of the arterial back yard to the progression and complications of atherosclerosis.

Reprint requests and correspondence: Dr. Amir Lerman, Division of Cardiovascular Diseases, Mayo Clinic Rochester, 200 First Street SW, Rochester, Minnesota 55905. E-mail: lerman.amir@mayo.edu.

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